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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,066	04/10/2001	Paul E. Nisson	0942.4800002/RWE/ALS	1532

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,066	NISSON ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/17/2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-71* is/are pending in the application.

4a) Of the above claim(s) *9-40 and 42-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on March 17, 2003 has been entered. The claims pending in this application are claims 1-4 and 6-71 with claims 9-71 withdrawn from consideration as the result of the restriction requirement. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on March 17, 2003. The following rejections are based on amendment.

Election/Restriction

2. This application contains claims 9-71 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-4, 6-8, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 is rejected as vague and indefinite because preamble (goal of the claim) and final product produced by method steps do not correspond each other. Note that final product

produced by method steps is a hybridized double stranded nucleic acid while preamble of the claim is directed to a method for denaturing or separating double-stranded nucleic acid molecule. Please clarify.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 2, 4, 6-8, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zarling *et al.*, (US Patent No. 5,719,023, 102 (e) date: June 3, 1994) in view of Aslanyan *et al.*, (Biophysics, 29, 615-620, 1984).

Zarling *et al.*, teach in situ hybridization method. As shown in Examples 2 and 3, a double stranded chromosome X alpha satellite DNA probe was heat denatured to become a single stranded before in situ hybridization. During the hybridization, a single stranded chromosome X alpha satellite DNA probe was hybridized with target nucleic acids in Hep-2 cell nuclei that immobilized in slides (see columns 17 and 18) as recited in step ii) of claim 1.

Zarling *et al.*, do not disclose to denature double stranded nucleic acid molecules using amino acid denaturants as recited in claims 1, 2, 4, 6-8 and 41.

Regarding claims 1, 2, 4, 6-8, and 41, Aslanyan *et al.*, teach the effect of glycine on conformation and thermal stability of DNA. As shown in Figures 1 and 2, glycine concentration with range of 1 mM- 3000 mM (log10=1000 mM, see Figure 1) as recited in claims 6-8 was shown to reduce the melting point of calf thymus DNA. The intermolecular interaction between DNA and glycine caused sharp fall in the enthalpy of the helix-coil transition and led to uncoiling of the DNA double helix (causing double stranded DNA to become single stranded as recited in claim 1) (see abstract in page 615, pages 616 and 617, and Figures 1 and 2). Glycine was considered as a natural amino acid denaturant as recited in claim 4 and 41.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of the prior art of Zarling *et al.*, and Aslanyan *et al.*. One having ordinary skill in the art would have been motivated to do so because Aslanyan *et al.*., have successfully used an amino acid denaturant (ie., glycine) to denature a double stranded nucleic acid probe into a single stranded and the simple replacement of

one well known denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Aslanyan *et al..*,) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

8. Claims 1-3 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zarling *et al.*, (June 3, 1994) in view of Yoshida (Biochem. Biophys. Res. Commun., 116, 217-221, 1983).

The teachings of Zarling *et al.*, have been summarized previously, *supra*.

Zarling *et al.*, do not disclose to denature double stranded nucleic acid molecules using an amino acid denaturant comprising polyamino acids as recited in claims 1-3 and 41.

Regarding claims 1-3 and 41, Yoshida teaches Mg^{2+}, Ca^{2+}-dependent unwinding of DNA by poly-L-glutamic acid. Figures 2-4 showed that the decrease of Tm of a double stranded DNA by poly-L-glutamic acid in the presence of Mg^{2+} or Ca^{2+} was due to the unwinding of DNA double-helix by poly-L-glutamic acid (see Figures 2-4 and first paragraph in page 220). poly-L-glutamic acid was considered as a polyamino acids comprising two or more amino acids as recited in claim 3 and an unnatural amino acid as recited in claim 41.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant comprising polyamino acids in view of the prior art of Zarling *et al.*, and Yoshida. One having ordinary skill in the art would have been motivated to do so because Yoshida has successfully used an amino acid denaturant (ie., poly-L-glutamic acid) to denature a double stranded nucleic acid probe into a single stranded and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Yoshida) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their

expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

9. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zarling *et al.*, (June 3, 1994) in view of Yoshida (1983) as applied to claims 1-3 above.

The teachings of Zarling *et al.*, and Yoshida have been summarized previously, *supra.*

Zarling *et al.*, and Yoshida do not disclose to use a concentration of amino acid denaturant as recited in claims 6-8. However, Yoshida showed integral thermal denaturation profiles of a double stranded DNA in the presence of different weight ratios of added poly-L-glutamic acid to the double stranded DNA such as 0.5 (see Figure 3). Since thermal melting transition of a double stranded DNA in a sample solution was measured in a 4 ml cell by a Beckman Acta CIII spectrophotometer (see page 218, fourth paragraph), when the weight ratio of added poly-L-glutamic acid to the double stranded DNA was 0.5 and the double stranded DNA was 300 μg in the sample solution, the concentration of the added poly-L-glutamic acid was 4.26 μM (150 μg in 4 ml of the sample solution).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used an amino acid denaturant with different concentrations in the method as recited in claim 1 in view of prior art of Zarling *et al.*, and

Yoshida. One having ordinary skill in the art has been motivated to do so because optimization of concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimize concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid. Note that, where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-4, 6-8, and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U. S. Patent No. 6,268,133 in view of *Zarling et al.,* (June 3, 1994) in view of Yoshida (1983).

Although claims 1-4, 6-8 and 41 in this instant application are much broader than claims 1-9 of U.S. Patent No.6,268,133 and have an additional step ii), claims 1-9 of U.S. Patent No.6,268,133 fall entirely within the scope of step I) of claim 1 and claims 2-9 of U.S. Patent No.6,268,133 are identical to claims 2-4, 6-8, and 41 of this instant application.

The teachings of Zarling *et al.*, have been summarized previously, *supra.* Zarling *et al.*, teaches step ii) of claim 1 (see above).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of U.S. Patent No.6,268,133 and the prior art of Zarling *et al.*. One having ordinary skill in the art would have been motivated to do so because U.S. Patent No.6,268,133 has successfully used an amino acid denaturant (ie., glycine) to denature a double stranded nucleic acid probe into a single stranded and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an amino

acid denaturant taught by U.S. Patent No.6,268,133) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

12. Applicant's arguments with respect to claims 1-4, 6-8, and 41 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. No claim is allowed.

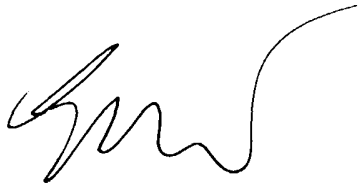
15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
May 27, 2003



Ethan Whisenant, Ph.D.
Primary Examiner (FSA)